first adjuvant including amorphous calcium phosphate (ACP) formulated as an injectable paste having a solids content of greater than 40 wt %. The high solids content of the adjuvant improves antigen adsorption and controlled delivery of the antigen.

The adjuvant composition may include a first adjuvant as a calcium phosphate composition and capable of hardening. The injectabiltiy and hardening ability of the adjuvant improves adjuvant delivery.

The adjuvant composition alternatively includes a first adjuvant including calcium phosphate, and a second adjuvant, wherein the first and second adjuvant are selected to elicit a immunological response of a specific immune cell-type. The use of a second adjuvant augments the effect observed in the primary adjuvant, either by enhancing a response in the same cell type or eliciting an immune response in a different cell type.

II. Amendments.

Claims 1, 13-15, 26-27, 33 and 37 are amended, and claims 38-44 are newly added.

Support for the amendment of claims 1, 13 and 14 is found on page 52, lines 1-2, where hydrated precursors containing amorphous calcium phosphate are disclosed, which have a solids content in the range of about 40-60 wt%.

Support for the amendment of claims 15, 26 and 27 are found on page 35, line 5-9; and in Examples 16 and 17 on pages 50-52.

Support for the amendment of claims 28 and 36 is found on page 7, line 19-page 8, line 3.

Support for newly added claim 38 is found on page 20, lines 1-17; support for claim 39 is found in original claim 15; support for claims 40-42 is found in Example 18, pp. 52-59; and support for claims 43-44 is found on page 37, lines 19-24, and page 38, lines 8-10. It is submitted that no new matter has been added.

III. The Office Action.

Claims 1-37 are pending in the above-identified application. Claims 1, 13-15, 26-28, 33 and 37 are amended; claims 4, 7, 9, 22 and 32 are canceled; and claims 38-44 are newly added. Claims 1-2, 6-7, 10, 11, 13-16, 19, 23, 24, 26-31 34, 35, and 37 stand rejected under 35 U.S.C. §102(b); and claims 1-37 stand rejected under 35 U.S.C. §103(a).

Applicants note that the effective date of this invention for the purpose of examination is September 15, 1998. Applicants reserve the right to establish an earlier priority date for any particular claim, if needed.

IV. Sec. 102(b) Rejections.

(A) Claims 1-14 directed to an ACP adjuvant.

Claims 1-2, 6-7, 10, and 13-14 stand rejected under 35 U.S.C. §102(b) as being anticipated by Towey et al, USP 2,967,802.

Claims 1-2, 6, 10-11, and 13-14 stand rejected under 35 U.S.C. §102(b) as being anticipated by Wilkinson et al., USP 4,110,432.

Claims 1-2, 6, 10-11, and 13-14 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gupta et al. (Vaccine Design, Ch. 8, pp 229-248 (1995)).

The Examiner considers that each of these references meets the limitations of the instant claims. Amended claims 1, 13 and 14 are directed to an adjuvant composition (or its use) comprising ACP which is formulated as a paste having at least a 40 wt% solids content. None of the cited references teach all of the recited features of the invention.

Towey describes a calcium phosphate gel which may be used as an adjuvant in the production of immunizing agents (col. 3, l. 54-56). The gel can contain as much as 15% solids, but is usually more dilute (col. 3, l. 15-16).

Wilkinson describes a prostaglandin conjugate with an immunogenic macromolecule complex (col. 1, l. 25-30) administered as a vaccine (col. 5, l. 53-54). The vaccine formulation may include calcium phosphate (col 6, l. 15-17). There is no teaching of using amorphous calcium phosphate (ACP), and specifically an injectable paste having a solids content of greater than 40 wt%. Referring to column 8, lines 10-25, the Examiner suggests that Wilkinson teaches compositions which are lyophilized to produce an amorphous powder (page 4, paragraph 5, of most recent Examiner Action); however, such statements regarding an amorphous lyophilized powder refer to the prostaglandin-bovine serum albumin (BSA) complex and not the adjuvant.

Gupta describes the formation of calcium phosphate gels having a pH of 5.7-6.1. It is known in the art that calcium phosphate precipitation under neutral or acidic conditions produces a crystalline apatitic calcium phosphate. The calcium phosphate gels described in Table IV have solid contents of about 0.2%, i.e., about 0.002 g calcium and phosphorous in 1 mL (1 g) of liquid.[1] There is no teaching of using amorphous calcium phosphate, and specifically there is no teaching of an ACP formulated as an injectable paste having a solids content of greater than 40 wt%.

For the foregoing reasons, it is submitted that none of the cited references teach all the features of the invention set forth in claims 1, 13 or 14. Claims 1, 13 and 14, and those claims dependent thereon are not anticipated by Towey, Wilkinson or Gupta.

(B) Claims 15-27 directed to a self-setting calcium phosphate cement.

Claims 15, 19, 23-24, and 26-27 stand rejected under 35 U.S.C. §102(b) as being anticipated by Wilkinson et al., USP 4,110,432.

Claims 15-16, 19, 23-24, and 26-27 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gupta et al. (Vaccine Design, Ch. 8, pp 229-248 (1995)).

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[1] This calculation does not take into account the presence of other atoms in the solid, e.g., oxygen and/or hydrogen; however, it is unlikely that the total solids content exceeds 1%.

The Examiner considers that each of these references meets the limitations of the instant claims. Amended claims 15, 26 and 27 are directed to an adjuvant composition (or its use) comprising a self-setting calcium phosphate composition which is formulated to harden. Neither of the cited references teach all of the recited features of the invention.

Gupta and Wilkinson are relied upon as described above in Section IV(A). Gupta describes gels of varying Ca and P content which gradually settle from solution (pp. 240-241). There is no teaching of a self-setting and hardenable calcium phosphate composition. In addition, the Examiner states (in page 4, paragraph 5, of the most recent Examiner Action) that Wilkinson discloses solutions that are prepared gradually over a period of one hour to obtain formulations having poorly crystalline characteristics (col. 8, l. 15-17); however, such a statement is made in reference to the prostaglandin-BSA complex and not the adjuvant composition.

Neither reference teaches a self-setting hardenable calcium phosphate cement adjuvant composition. For the foregoing reasons, it is submitted that none of the cited references teach all the features of the invention set forth in claims 15, 26 and 27. It is submitted that claims 15, 26 and 27 and those claims dependent thereon are not anticipated by Wilkinson or Gupta.

(C) Claims 28-37 directed to a two-component adjuvant.

Claims 28-31, 34, and 37 stand rejected under 35 U.S.C. §102(b) as being anticipated by Towey et al, USP 2,967,802.

Claims 28-30, 34-35, and 37 stand rejected under 35 U.S.C. §102(b) as being anticipated by Wilkinson et al., USP 4,110,432

Claims 28-30, 34-35, and 37 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gupta et al. (Vaccine Design, Ch. 8, pp 229-248 (1995)).

The Examiner considers that each of these references meets the limitations of the instant claims. Amended claims 28 and 37 are directed to an adjuvant composition (or its

use) comprising a first calcium phosphate adjuvant and a second adjuvant, wherein the first and second adjuvant are selected to elicit a immunological response of a specific immune cell-type. None of the cited references teach all of the recited features of the invention.

Neither Towey nor Wilkinson disclose the use of a calcium phosphate adjuvant and a second adjuvant. Gupta discloses that aluminum compounds have been used with other "adjuvant-active components from pertussis organisms, lipopolysaccharides and pertussis toxin" (p. 241, Sec. 4). There is no teaching of combining a calcium phosphate adjuvant with a second adjuvant.

The Examiner suggests that the prostaglandin conjugate with an immunogenic macromolecule represents an endogenous or exogenous enhancing agent of the invention. The Wilkinson conjugate increases the immunogenic response *in the antigen*, here prostaglandin, in a process known as haptenization. In contrast, the present invention is directed to modifications *of the adjuvant* to augment adjuvanticity. These are two different methods of modulating an immunogenic response in a composition.

For the foregoing reasons, it is submitted that none of the cited references teach all the features of the invention set forth in claims 28 and 37. It is submitted that claims 28 and 37 and those claims dependent thereon are not anticipated by Towey, Wilkinson or Gupta.

V. Sec. §103(a) Rejections.

Claims 1-37 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Relyveld (USP 4,016,252), Gupta et al., Wilkinson et al., and Kossovsky (USP5,462,751). Generally, the cited references teach use of calcium phosphate in adjuvant compositions. The examiner suggests that one skilled in the art would have been motivated to combine the various features of the prior art to obtain the claimed

invention. Applicants respectfully disagree.

Gupta and Wilkinson are relied upon as discussed above in Section IV.

Relyveld discloses a calcium phosphate gel having primarily a tricalcium phosphate composition. (col. 2, l. 38-43) The gels are of very low solids content, i.e., less than 1% (see, col 4, l. 1-17). Even in a concentrated form, gels are not available at solids contents above about 4 wt%. See, col. 9, l. 24-31. There is no discussion of self-setting calcium phosphate compositions, or the use of a second adjuvant.

Kossovsky discloses nanocrystalline particles of brushite (col. 3, l. 57-59), which are treated with a biocompatible coating used to anchor enzymes and other proteins without denaturing them. The coated particle is not an adjuvant, but serves as a substrate to deliver the attached enzyme, for example, as a decoy virus. Note, for example, in Example 5 where Epstein-Barr Virus Decoys are tested for elicitation of antibodies, the injected nanoparticles are "free of adjuvant" (col. 14, l. 54).

(A) Rejection of claims directed to ACP adjuvant.

Claims 1, 13 and 14 are directed to an adjuvant composition (or its use) comprising ACP which is formulated as a paste having at least a 40 wt% solids content. The high solids content of the instantly claimed adjuvant provides a large surface area on which antigens and other agents may be absorbed. Furthermore, the injectable paste formulation permits administration by injection, and aids in the continuous and extended depot delivery or the antigen or other factor.

None of the cited references teach or suggest an adjuvant composition having the recited high solids content of the amorphous calcium phosphate adjuvant of the invention. Nor do any of the references suggest the desirability of a high solids content injectable paste as the platform for an adjuvant composition. Gupta and Relyveld use gels of less than 10 wt %. Wilkinson provides no guidance as to any preferred adjuvant composition, other than that it contain a calcium phosphate. Kossovsky does not teach an adjuvant

composition.

For the foregoing reasons, it is submitted that there is no teaching or suggestion in the cited art for the invention as set forth in claims 1, 13 and 14, and those claims dependent thereon.

(B) Rejection of claims directed to a self-setting calcium phosphate composition.

Claims 15, 26 and 27 are directed to an adjuvant composition (or its use) comprising a self-setting calcium phosphate composition which is formulated to harden. The invention is directed to an advantageous composition which may be formed with a paste consistency and hardened *in vivo*. The hardening ability of the adjuvant provides for a depot which retains its physical integrity *in vivo* and improves adjuvant delivery. It also facilitates adsorption of the antigen or active agent on the solid calcium phosphate.

There is no appreciation of any of these features in the adjuvant compositions described in the cited references. Gupta and Relyveld disclose finely suspended calcium phosphate particles which slowly settle from a supernatant liquid to give a low solids content gel. These compositions are inherently incapable of hardening due to their high liquid contents. Wilkinson provides a generic teaching of a calcium phosphate adjuvant and does not suggest the significant modifications required of the prior art in order to obtain a self-setting calcium phosphate cement. Kossovsky is irrelevant to the claimed invention, as it also does not disclose or suggest a self-setting calcium phosphate composition.

For the foregoing reasons, it is submitted that there is no teaching or suggestion in the cited art for the invention as set forth in claim 15, 26 or 27, and those claims dependent thereon.

(C) Rejection of claims directed to a two-adjuvant composition.

Claims 28 and 37 are directed to an adjuvant composition (or its use) comprising a first calcium phosphate adjuvant and a second adjuvant, wherein the first and second

adjuvant are selected to elicit a immunological response of a specific immune cell-type. The examiner refers to Gupta for teaching that aluminum compounds have been used with other adjuvants, so that it would have been obvious to combine calcium phosphate adjuvant with additional adjuvants, as well.

Gupta does not provide any guidance as to the selection of the second adjuvant, and a fair reading of Gupta would suggest that there is no particular preference of a second adjuvant. In contrast, the instantly claimed invention requires selection of the second adjuvant such that an immunological response of a specific cell type is elicited. This reflects the appreciation that calcium phosphates are capable of eliciting a response from specific cell types. This recognition is first shown in Example 18 of the instant application.

As is recognized in Gupta, calcium phosphate is more biologically compatible than aluminum compounds. While this may make calcium phosphate an attractive alternative adjuvant to aluminum compounds, it also may have the undesired effect of providing a more muted immunological response. For the first time, the present invention recognizes that such subtleties in performance may be exploited by combining two adjuvants to elicit specific immunological responses.

For the foregoing reasons, it is submitted that claims 1-44 are patentable over the cited art. A favorable notice to that effect is requested.

VI. Miscellaneous.

Enclosed is a petition to extend the period for replying for three months, to and including June 17, 2000. Also enclosed is a check in the amount of $435.00 to cover the cost of additional claims. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: June 16, 2000

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